Economic Impact of Reducing Inappropriate Inhaled Corticosteroids Use in Patients With Chronic Obstructive Pulmonary Disease

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ABSTRACT

OBJECTIVES: To assess the budget impact of restricting inappropriate inhaled corticosteroids (ICS) use according to the international Chronic Obstructive Lung Disease (GOLD)-guidelines indication for ICS use in the Chronic Obstructive Pulmonary Disease (COPD)-population, taking The Netherlands as a reference case.

METHODS: A budget impact model was developed and closely aligned with the ISPOR best practice guidelines. The model estimates the impact of pharmacologic COPD maintenance treatments on clinical events (exacerbations and pneumonias) and associated healthcare utilization & costs. Current treatment mix included all maintenance treatments including long-acting muscarinic antagonists (LAMA), long-acting β2-agonists (LABA), LABA/ICS, LABA/LAMA, and triple therapy (LABA/LAMA/ICS). We modelled a situation where 25% of patients would use ICS-containing treatments and compared this to the current Dutch situation with 60% ICS use. A 5-year time horizon with a Dutch health care payer's perspective was used. In sensitivity analyses, a range of values for absolute ICS reduction (20-40%), relative risks of exacerbations and pneumonia events, and other input parameters were explored.

RESULTS: Over a period of 5 years, the new treatment mix with GOLD guideline recommended ICS and LABA/LAMA use resulted in potential avoidance of 17,405 exacerbations, 11,984 pneumonias and accompanied savings of €84 million in the base-case scenario. Savings were consistent in various sensitivity analyses, indicating cost savings between €30 and €200 million.

CONCLUSION: Reducing inappropriate ICS use and increased use of LABA/LAMA in COPD patients could result in a reduction of exacerbations and pneumonias, corresponding with a reduction in total costs for COPD in the Netherlands.

HIGHLIGHTS

i. What is already known about the topic? Unnecessary use of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) patients is prevalent and associated with potentially avoidable adverse drug reactions, yet its economic impact is unknown**.**

ii. What does the paper add to existing knowledge? Tailoring ICS use to the COPD population indicated by international GOLD guidelines can result in significant clinical and economic benefits on a Dutch national level.

iii. What insights does the paper provide for informing health care-related decision making? Reducing ICS use in patients with COPD has substantial budget impact and is mainly driven by avoidance of costly ICS adverse drug reactions. Careful targeting of ICS to the COPD population in need and active deprescribing in current over-users should be encouraged not only from a clinical, but also economic perspective.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually by significant exposure to noxious particles or gases".[1]

Worldwide, over 174 million patients suffer from COPD, causing 3.2 million deaths in 2015.[2,3] In the Netherlands, more than half a million patients are suffering from COPD, with a considerable impact on the Dutch national health budget: over €1 billion in 2015.[4–7] Notably, costs for COPD mostly involve hospitalizations, medication, nursing home care, and productivity losses.[8,9]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines make use of the "ABCD classification" for categorizing patients and selecting treatment.[1] Symptoms and exacerbation history are used in determining the severity of COPD and the recommended medication. In GOLD A patients, (short or long-acting) bronchodilators are indicated, while in GOLD B patients, a long-acting muscarinic antagonist (LAMA) or a long-acting β2-agonist (LABA) is recommended. In patients with GOLD C a LAMA is recommended and in GOLD D, that is, symptomatic patients who experience two or more moderate exacerbations (or one severe exacerbation) within a year and high blood eosinophil counts, inhaled corticosteroids (ICS) can be considered.[1]

ICS have been shown to reduce exacerbations in various trials and can be administered next to a LAMA or LABA, or as part of fixed-dose combination inhaler together with a LABA or triple therapy (LAMA/LABA/ICS).[10–17] However, ICS can also cause some serious adverse drug reactions(ADRs), such as pneumonia, dysregulated diabetes control and osteoporosis, as well as less serious but still significant local ADRs, such as oropharyngeal candidiasis, pharyngeal discomfort, cough and hoarseness. [18–23] In recent years, the mere use of LAMA/LABA combination therapy (i.e. without ICS) in COPD has been shown beneficial.[10,15,24] To reflect this new evidence, the GOLD guidelines have been updated and recommend careful consideration of clinical benefits versus risks regarding ICS use.[1]

Despite recommendations of conservative use of ICS in recent guidelines, in real-life, ICS are still used in many COPD patients that do not meet the aforementioned criteria.[25–28] This non-adherence to COPD guidelines may not only result in potential side effects, but may also have economic consequences, although the latter has not been researched to date. Notably, a recent systematic review on COPD cost-effectiveness studies identified the incorporation of ADRs in

economic models, such as those arising from ICS, as an unmet need in COPD cost research.[29] In addition, few budget impact analyses (BIAs) of COPD treatments have been published to date.[29–31]

The objective of this study was to assess the budget impact of following the GOLD COPD guideline recommendations regarding ICS prescription, taking the Netherlands as a reference case.

METHODS

Study design

A BIA was performed following the ISPOR Task Force Report, BIA-Principles of Good Practice designed within the context of an Excel-based cost-calculator model.[32,33] The cost-calculator enables the calculation of the impact of different pharmacologic COPD maintenance treatments on clinical respiratory events (exacerbations, pneumonias) and associated healthcare resource utilization – in this context, respiratory events are calculated using the relative risks (RR) associated with each treatment group. A brief review of the key elements in the ISPOR BIA-Principles of Good Practice is presented in Supplementary table 1, with an indication where we included its specific segments in our analysis. The model specifics are described in the following sections.

Patient population

The population considered in this analysis consists of COPD patients belonging to GOLD B, C and D classes, the population that may eligible for ICS treatment. As data on treatment use is not available per GOLD A-D class for the Netherlands, no stratification was possible for the GOLD classes in the model. GOLD A patients are excluded because there is no clinical benefit in treating them with ICS in clinical practice.[1,25,34] Estimations of the total number of Dutch patients belonging to this population were taken from Dutch national published sources and reported in Table 1.[35,36] The size and growth of the Dutch COPD population was taken from the health exploration report of the Dutch public health institute (RIVM), which estimated the trends in morbidity and mortality of COPD for the next decades, primarily using primary care diagnostic data.[6]

Intervention mix

The intervention considered in this model is pharmacological COPD maintenance treatment, with the current treatment mix for the COPD population including LAMA, LABA/ICS, LAMA/LABA, LAMA/LABA/ICS and other. LAMA/LABA/ICS was recently launched as fixed-dose "triple therapy" in the Netherlands.[37] We assumed patients on other medication were using LABA therapy.

We estimated market shares for the current maintenance treatment mix from national public sources, which we adjusted for the situation in 2017 by extrapolating market trends.[17,38] The current percentage of patients using ICS-containing regimens was 60.2%. The market share for the triple therapy was estimated at 38.4% based on the concurrent use of LABA/ICS and LAMA. Similarly, a UK real-world study showed a proportion of 32% patients using triple therapy.[39]

In the new intervention mix, 25% of GOLD B-D patients was assumed to be remaining on ICS therapy, in line with the percentage of COPD patients with GOLD criteria for ICS use. This was achieved by switching 75% of LABA/ICS users and 50% of LABA/LAMA/ICS users to LABA/LAMA treatment. Indeed, in the most recent guidelines, GOLD recommends ICS explicitly in patients with high (>300 cells/mm^3) eosinophil counts, which is present in +/-20% of the COPD population.[1,40,41] Yet, to also account for other risk groups where ICS may be beneficial (e.g. frequent exacerbators, asthma-overlap.[1,40–45]), we considered a slightly higher percentage of ICS (i.e. 25%) in the new treatment mix. Note that these additional criteria could partly overlap (e.g. those COPD patients with high eosinophils may also have asthma overlap and have better ICS response in preventing exacerbations). Given the uncertainty around this conservative estimate, this assumption of 25% was extensively explored in sensitivity analyses (see later section).

Time horizon

A five year time horizon was used, in line with relevant planning horizons of Dutch policy makers, and ISPOR BIA-Principles of Good Practice.[32] Results are presented annually, starting from the year 2017, up to 2021. No discounting was applied.[32]

Perspective

This BIA was performed from a Dutch health care payer's perspective. This choice implicates inclusion of only direct health care costs; i.e. medications, hospitalizations, emergency room visits and ambulatory visits. Given the BIA guideline recommendation as well as the scarcity of data on impact on indirect costs (e.g. work productivity losses), these were not considered.[32]

Analytic framework description

The population GOLD B-D patients entering the cost calculator concerns all COPD patients using LAMA, LAMA/LABA, LABA/ICS, LAMA/LABA/ICS or other. The graphical description of the model structure is shown in Figure 1. The distribution of the population is given per treatment group. Costs inputs concern the pharmacological treatment costs, moderate and severe exacerbations, pneumonia, and diabetes-related events. Incidence rates of these events are stable across the five-year time horizon, although the actual number of events varies due to the changing exacerbation history and the in- and efflux of patients in the model. Notably, given the limited amount of data for diabetes-related hospitalizations, as well as their low occurrence (0.1-1%), these events were excluded from the base-case and only assessed in an alternative scenario analysis.[46] Given the limited body of evidence that suggests a difference in cardiovascular events between the different included treatment options, these were excluded from the model. [47–49] Ergo, clinical events included in the base-case only concerned pneumonias and exacerbations.

Figure 1: Model flow chart

Inputs and data sources

All model input data are provided in Table 1. National Dutch data on COPD was identified through a keywords literature search in Medline (PubMed) and Embase. In addition, Dutch health related online sources were searched for relevant data. For all imputed costs we used Dutch data, and values given in price levels different from 2017 were inflated accordingly. [35,50,51]

The patient population size was based on national data sources and was extrapolated to reflect the COPD population over the period 2017 to 2021. Incidence and mortality estimates were already included in the extrapolated population numbers.[4] To reflect the Dutch patient group belonging to GOLD B-D, we considered 72% of the total diagnosed

COPD population, as published in a national report that labels 28% as GOLD A.[36] Input data for exacerbations [10,31,52–55], pneumonia [21,51,56] and diabetes-related hospitalizations [23,56,57] were based on published data. Complication rates and cost calculations for exacerbations, pneumonias and diabetes are specified in the next sub- sections.

Exacerbations

LAMA/LABA users with no prior exacerbations were the reference case and RRs were estimated as compared to that group. For the base-case, RR data were derived from recent meta-analyses, comparing LAMA/LABA maintenance therapy to triple therapy[58], LABA/ICS[59] and LAMA monotherapy[48]. We assumed equal RRs across populations belonging to GOLD B-D.[52]

Absolute annual exacerbation risk was estimated using risk of any exacerbation for GOLD B patients in the TONADO trial (39.4%).[55] Additionally the rates were used of moderate (78%) and severe (16%) exacerbations within the GOLD B/C sub-population of LAMA/LABA users with fewer than two exacerbations.[55,60] This resulted in an annual absolute risk of 31% for moderate, and 6% for severe exacerbations (Table 1).

Exacerbation history was assumed to have equal impact on both moderate and severe exacerbation risk. At baseline, we assumed equal exacerbation frequency proportions across the therapeutic options, resulting in 53% of patients with no exacerbations, 25% of patients with one exacerbation and 22% of patients with two or more exacerbations.[52] Exacerbation rates were dependent on absolute annual risk, exacerbation history and type of maintenance therapy used.[31]

Pneumonia

Pneumonia event risks were based on a meta-analysis of five recent trials comparing the pneumonia rates of LAMA/LABA users and LAMA/LABA/ICS users.[58] We used a pneumonia rate of 4.7% in the control group and added a RR of 1.31 for ICS users.[21,58]

Diabetes

Data on risk for diabetes-related hospitalizations were derived from a cohort study of COPD patients with comorbid type II diabetes.[23] We used the Dutch national prevalence of 20.9% COPD patients having diabetes (Table 1).[57] Primary

care and medication costs, such as General Practitioner (GP) visits and a faster progression to insulin treatment, were not considered.[23]

Costs inputs

The annual costs of pharmacological treatments were calculated using Dutch national real-world reimbursement data, reflecting the average of all users within each drug class in the Netherlands for the year 2017.[17] Event costs for exacerbations were based on previously published cost estimations, considering both moderate and severe exacerbations using weighted averages for resource use, ranging from hospitalizations to prescribed antibiotics and/or oral corticosteroids in the GP setting.[31,61] Per event costs for pneumonia were calculated as a proportion of inpatient (28%) and outpatient (72%) events[51], using Dutch open data of reimbursed costs in the healthcare system (open DIS data).[56] Diabetes-related hospitalizations were calculated similarly; a weighted average was calculated for one hospitalization, taking into account the length of stay.[56]

Table 1: Input data for the BIA model

Analyses

Using the cost calculator, we assessed the budget impact for the future treatment mix scenario with reduced use of ICS.

Therapy prices were assumed to be subject to an annual reduction of 3% across all therapeutic options. [64]

Uncertainty and scenario analyses

As evidence on the clinical effectiveness regarding exacerbation reduction and pneumonia risk of LABA/LAMA compared to triple therapy and LABA/ICS varies, we performed a sensitivity analysis taking into account a range of RRs and included these in separate figures; the point estimates of various clinical trials were included in the figures as well.

Additionally, various key model inputs were varied and presented in a tornado diagram. This included scenarios where the percentage of patients remaining on ICS treatment was altered to both 20%, 30% and 40%; scenarios where only

LABA/ICS or only LAMA/LABA/ICS use was reduced; and scenarios where the total COPD population was assumed to be 700.000 or 500.000. Lastly, a scenario with inclusion of diabetes-related hospitalizations was included.

RESULTS

Clinical impact

When reducing ICS use within the Dutch COPD GOLD B-D population to 25% and increasing the use of LABA/LAMA therapy, both the number of exacerbations and pneumonia events decreased. Over a five-year period, the number of exacerbations decreased from 1,796,385 to 1,778,980, i.e. a decrease of 17,405 exacerbations or around 9 exacerbations per day. The number of pneumonia events was lowered by 11,984 (from 129,034 to 117,050) over five years or around 6 daily occurrences of pneumonia. The clinical impact of prevented exacerbations and pneumonia events by appropriate ICS use is displayed in Figure 2; the disaggregated numbers of events are given in Supplementary table 2.

Economic impact

The new treatment mix, with reduced ICS use, resulted in lower budget impact compared to the 2017 intervention mix (Figure 2). Total costs for the 2017 intervention mix were estimated at €596 million and in the new mix at €579 million, with corresponding numbers for the whole 5-year follow-up period of €3.01 and €2.93 billion respectively. As such, the total 5-year savings are estimated at €84 million, i.e. around 3% of the total COPD costs. A complete overview of the disaggregated annual costs and savings are given in Supplementary table 3.

Figure 2 shows the economic effects of the new intervention mix scenario to the budget impact, associated with pharmacological treatment, exacerbations and pneumonia. The reduction in pharmacological treatment costs in the new intervention mix scenario has the largest impact on COPD spending, followed by the costs associated with pneumonia.

Figure 2 – Budget impact of inhaled corticosteroid reduction in COPD patients, presented by total and disaggregated cost savings over a 5-year follow-up

Sensitivity analyses

Figure 3 shows the effects of varying the RRs for exacerbations of LABA/LAMA/ICS and LABA/ICS, with LABA/LAMA as the reference on the budget impact, including the means of a variety of relevant trials. In all

alternative scenarios, limiting ICS use resulted in cost savings, even when data from the trial that showed the largest benefit for triple therapy, IMPACT, was used.[11] Only at RRs for exacerbations lower than 0.7, additional costs will occur. For LABA/ICS compared to LABA/LAMA, the RR would have to drop below 1 before the new intervention mix would yield additional costs, but this is highly unlikely, considering the evidence from clinical trials.[10,16,59] If the most conservative available evidence is used, i.e. the IMPACT trial for LABA/LAMA vs. triple therapy and the FLAME trial for LABA/LAMA vs. LABA/ICS, the budget impact still results in net cost savings of €30 million.[10,11] Using the least conservative numbers, i.e. the WISDOM and LANTERN trials, results in total net savings of €200 million.[15,16] The effect of the RRs of pneumonia caused by ICS-use is shown in Figure 4. For the whole range of RRs considered, the budget impact remains cost-saving.

Figure 3 – Sensitivity analysis detailing the effect of varying the relative risk of exacerbations (LAMA/LABA/ICS vs. LABA/LAMA and LABA/ICS vs. LABA/LAMA) on the 5-year budget impact of appropriate inhaled corticosteroids use in COPD patients, including the point estimate of various clinical trials[10–16] *IMPACT: Informing the Pathway of COPD Treatment trial; TRIBUTE: Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease trial; OPTIMAL: Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease trial; SUNSET: Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease trial; WISDOM: Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management trial; FLAME: Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD trial; LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD trial.*

Figure 4 – Sensitivity analysis detailing the effect of varying the relative risk of pneumonia (ICS use vs. non-ICS use) on the 5-year budget impact of appropriate inhaled corticosteroids use in COPD patients, including the point estimates of various trials[11–15] *IMPACT: Informing the Pathway of COPD Treatment trial; TRIBUTE: Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease trial; OPTIMAL: Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease trial; SUNSET: Long-Term Triple Therapy De-escalation to*

Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease trial; WISDOM: Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management trial.

Figure 5 shows the various alternative scenario analyses. The alternative scenario with diabetes-related hospitalizations being included resulted in 2,591 avoided hospitalizations in five years, corresponding to €10 million of extra savings in 5 years. The savings of only reducing either triple therapy or LABA/ICS therapy separately are comparable, both around €42 million. Reducing or increasing the COPD population, also reduces or increases the budget savings. The ICS-use reduction impacts the model considerably, if 40% of GOLD B-D patients remain on ICS, the total 5-year savings decrease to €47 million, or €71 million for 30%; if 20% of patients remain on ICS, the savings increase to €95 million.

Figure 5 - Tornado diagram representing the 5-year savings achieved by reducing ICS-containing regimens in COPD in different scenarios. *LABA, long-acting β2-agonists; LAMA, long-acting muscarinic antagonists; ICS, inhaled corticosteroids.*

DISCUSSION

Main findings

Reducing the use of ICS-containing treatments, while increasing the LABA/LAMA use in COPD patients in the Netherlands, as indicated by the GOLD guidelines, could lead to cost savings of €84 million over a period of five years, while reducing the number of exacerbations by 17,405 and pneumonia-related events by 11,984. The main drivers for budget impact were lower pharmacological treatment costs and costs associated with avoided exacerbations and pneumonia events.

Interpretation

A recent Dutch budget impact study, focusing on the introduction of LABA/LAMA therapy, estimated the total annual COPD costs for the period 2015-2019 to increase from €489 to €663 million, considering costs for medications, management and exacerbations.[31] Our annual estimations for the COPD budget in the period from 2017 to 2021 ranged from €580 to €610 million which seem in line with these previous projections.[7] The new intervention mix with reduced ICS use under base-case assumptions resulted in cost-savings within the COPD budget of around 3% (annually and over 5 years). The total COPD budget, which currently accounts for about 0.6% of healthcare spending in the Netherlands, could stay flat or even decline in the coming years.[35] Compared to earlier Dutch COPD budget estimations, our estimations are similar. [7,31] However, all budget estimates were based on slightly different methodologies and costs categories. Unlike previous publications, we considered ADR-related costs. [7,31] Additionally, differences in total expenses can be explained by the year of calculation, and the total size of the COPD population, which has increased considerably in recent years.[6,7,36]

Due to a lack of previous publications focusing on the economic impact of ICS reduction, we were not able to compare our results. Yet, recent clinical evidence supports our results.[24] Indeed, studies showed a decreased number of exacerbations and pneumonia events in patients who switched from LABA/ICS to LABA/LAMA.[59,65] Another two studies comparing LABA/ICS with LABA/LAMA showed comparable safety profiles and higher incidence of pneumonia in the LABA/ICS treated patients.[66,67] Furthermore, a Swedish study demonstrated lower costs and better outcomes when patients were using LABA/LAMA vs LABA/ICS.[68]

An older meta-analysis comparing LABA/LAMA and LABA/ICS, not used in our model study, showed a reduction in the incidence of pneumonia (8%) with use of LABA/LAMA.[69] Our results are quite close with a 9% reduction of pneumonia events. This small difference may be caused by our consideration of all four available LABA/ICS treatment options in the Netherlands (salmeterol/fluticasone; formoterol/budesonide; formoterol/beclomethasone and vilanterol/fluticasone), while the meta-analysis considered only salmeterol/ fluticasone.

Strengths and limitations

To our knowledge, this is the first BIA considering the budget impact of reducing ICS-use in patients with COPD. This BIA complied with ISPOR's BIA-Principles of Good Practice with respect to the reporting format and content.[32]

The time horizon we used is in line with both ISPOR's recommendations as well as relevant planning horizons of Dutch policy makers and Dutch guideline for economic evaluations in healthcare.[50]

While the effects of additional ICS treatment vary between clinical trials, our results seem robust to these variations, as the reduction in ICS use remained cost-saving, independent of the clinical trial used. This was also the case when we reduced the rate of pneumonia events caused by ICS use.

A limitation of this study is the uncertainty regarding the COPD population in the Netherlands. While most estimations are within the same range, these estimates are usually based on primary care diagnosis codes.[57] Some patients with a COPD coding may not have spirometry confirmed COPD, which is the gold standard for proper diagnosis.[4,6,7,36,70] Notably, relying on COPD codes only may result in misclassified patients, underdiagnosis or overdiagnosis. We were also not able to incorporate the GOLD classes separately, due to a lack of detailed data on specific event rates and RRs per GOLD class. Additionally, there is some uncertainty on the percentage that benefits from remaining on ICS treatment, as data on the demographics and associated treatment regimes in the Netherlands of specific subgroups are not currently available, such as the proportion of patients with asthma or blood eosinophil counts (>300 cells/mm^3).[40,41] The sensitivity analysis shows a considerable impact of the proportion of patients that continues to use ICS treatment on the budget impact difference; with a 5% decrease or increase of this proportion resulting in around a 15% increased or decreased budget impact difference respectively.

Exacerbation history was assumed to be the same across the various treatment options, although we would suspect patients with triple therapy to have had more exacerbations in the past, as compared to e.g. LAMA monotherapy users. This marks a limitation in our analysis, as we were unable to find the necessary data to incorporate this difference in our analysis.

Lastly, while this study mainly focused on the ADRs of ICS-treatments, non-ICS containing regimens such as single or dual bronchodilators could also give rise to ADRs, mainly in the cardiovascular area. According to a recent meta-analysis, possible ADRs were atrial fibrillation (0.39%), myocardial infarction (0.27%), and coronary artery disease (0.26%).[71] Several meta-analyses have been published that looked into the cardiovascular effects of COPD inhalation treatment, but event rates were low and significant differences between treatment options have not been found.[47–49] While this might impact absolute budget impact, the relative budget impact is not expected to be affected by this, considering there would be no difference caused by changing prescribing behaviour of ICS especially as these are usually prescribed in fixed-dose combination with LABA. Less serious ADRs, such as oropharyngeal candidiasis, pharyngeal discomfort, cough and hoarseness were also not included in the analysis, due to the minimal economic impact.

Implications for practice and policy

Given the substantial clinical and economic savings that could be achieved from restricting ICS use to the guidelines-indicated COPD population, we recommend careful targeting of ICS to the COPD population in need and active deprescribing in current over-users should be encouraged. [1] Furthermore, exploring the reasons for inappropriate use of ICS treatments in real-life may be beneficial to identify strategies to stimulate shifts to non-ICS treatments. Still, improvements can be made in the adherence to the COPD guidelines by doctors: a Dutch study reported inappropriate prescribing for ICS treatments in 30% of COPD patients.[72] Studies from the United Kingdom reported inappropriate ICS prescribing in 25% and 43% of COPD patients. [26,73] Similarly, an Australian study indicated 44% inappropriate use of ICS treatments.[74]

Preventing ICS overuse in COPD patients could be achieved by improved education of healthcare professionals, better promotion of therapy guidelines and improved diagnostic tools.

Conclusions

Reducing inappropriate ICS use and increased use of LABA/LAMA in COPD patients could result in a reduction of exacerbations and pneumonias, corresponding with a reduction in total costs for COPD in the Netherlands.

References

1. Global Initiative for Chronic Obstructive Lung Disease. *Pocket Guide to COPD Diagnosis, Mangement and Prevention - 2019*. Global Initiative for Chronic Obstructive Lung Disease; 2018. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-DRAFT-v1.7-14Nov2018-WMS.pdf. Accessed January 11, 2019.

2. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *LancetRespiratory Med*. 2017;5(9):691-706.

3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3(11):e442.

4. Nederlands instituut voor onderzoek van de gezondheidszorg. COPD. https://www.volksgezondheidenzorg.info/onderwerp/copd. Accessed November 6, 2018.

5. Rijksinsituut voor Volksgezondheid en Milieu (RIVM). Costs of Illness Tool. https://statline.rivm.nl/#/RIVM/nl/dataset/50040NED/table?graphtype=Table&ts=1512975518824. Published December 11, 2017. Accessed January 10, 2019.

6. RIVM. Aandoeningen. Volksgezondheid Toekomst Verkenning. https://www.vtv2018.nl/aandoeningen. Published 2018. Accessed November 26, 2018.

7. Suijkerbuijk AWM, Wijga AH, Heijmans M, et al. Societal costs of asthma, COPD and respiratory allergy. *Ned Tijdschr Geneeskd*. 2013;157(46):A6562-A6562.

8. Suijkerbuijk AWM, Hoogeveen RT, De Wit GA, et al. Maatschappelijke kosten voor astma, COPD en respiratoire allergie. 2013;(Journal Article).

9. Van Boven JFM, Vegter S, Van Der Molen T, Postma MJ. COPD in the working age population: the economic impact on both patients and government. *COPD J Chronic Obstr Pulm Dis*. 2013;10(6):629-639.

10. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. *N Engl J Med*. 2016;374(23):2222-2234. doi:10.1056/NEJMoa1516385

11. Lipson DA, Barnhart F, Brealey N, et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med*. 2018;378(18):1671-1680. doi:10.1056/NEJMoa1713901

12. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *The Lancet*. 2018;391(10125):1076-1084. doi:10.1016/S0140-6736(18)30206-X

13. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146(8):545-555.

14. Chapman KR, Hurst JR, Frent S-M, et al. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *Am J Respir Crit Care Med*. 2018;198(3):329-339. doi:10.1164/rccm.201803-0405OC

15. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med*. 2014;371(14):1285-1294. doi:10.1056/NEJMoa1407154

16. Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2015;10(Journal Article):1015-1026. doi:10.2147/COPD.S84436

17. Zorginstituut Nederland. GIP Databank. GIP Databank. https://www.gipdatabank.nl/. Published 2018. Accessed November 6, 2018.

18. Matera MG, Cardaci V, Cazzola M, Rogliani P. Safety of inhaled corticosteroids for treating chronic obstructive pulmonary disease. *Expert Opin Drug Saf*. 2015;14(4):533-541.

19. van Boven JFM, Vegter S. Inhaled corticosteroids and the occurrence of oral candidiasis: a prescription sequence symmetry analysis. *Drug Saf*. 2013;36(4):231-236.

20. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J*. 2012;22(1):92.

21. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169(3):219-229.

22. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax*. 2013;68(6):540-543. doi:10.1136/thoraxjnl-2012-202709

23. Price DB, Russell R, Mares R, et al. Metabolic effects associated with ICS in patients with COPD and comorbid type 2 diabetes: a historical matched cohort study. *PloS One*. 2016;11(9):e0162903.

24. Worth H, Buhl R, Criée C-P, Kardos P, Lossi NS, Vogelmeier CF. GOLD 2017 treatment pathways in 'real life': An analysis of the DACCORD observational study. *Respir Med*. 2017;131:77-84. doi:10.1016/j.rmed.2017.08.008

25. Snoeck-Stroband JB, Schermer TRJ, van Schayck CP, et al. NHG-Standaard COPD (Derde herziening). *Huisarts En Wet*. 2015;58(4):198-211.

26. White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids-implications for safety and costs: cross-sectional observational study. *PLoS One*. 2013;8(10):e75221.

27. Seaman J, Leonard AC, Panos RJ. Health care utilization history, GOLD guidelines, and respiratory medication prescriptions in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2010;5(Journal Article):89-97.

28. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis*. 2014;9:889-904. doi:10.2147/COPD.S62750

29. van der Schans S, Goossens LM, Boland MR, et al. Systematic review and quality appraisal of cost-effectiveness analyses of pharmacologic maintenance treatment for chronic obstructive pulmonary disease: methodological considerations and recommendations. *PharmacoEconomics*. 2017;35(1):43-63.

30. van de Vooren K, Duranti S, Curto A, Garattini L. A critical systematic review of budget impact analyses on drugs in the EU countries. *Appl Health Econ Health Policy*. 2014;12(1):33-40.

31. van Boven JFM, Kocks JW, Postma MJ. Cost-effectiveness and budget impact of the fixed-dose dual bronchodilator combination tiotropium-olodaterol for patients with COPD in the Netherlands. *Int J Chron Obstruct Pulmon Dis*. 2016;11(Journal Article):2191-2201. doi:10.2147/COPD.S114738

32. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014;17(1):5-14. doi:10.1016/j.jval.2013.08.2291

33. Microsoft. *Excel*. Redmond, WA, United States; 2018. https://www.office.com/.

34. Mirza S, Clay RD, Koslow MA, Scanlon PD. COPD Guidelines: A Review of the 2018 GOLD Report. *Mayo Clin Proc*. 2018;93(10):1488-1502. doi:10.1016/j.mayocp.2018.05.026

35. Statistics Netherlands. CBS StatLine. Statline. http://statline.cbs.nl/Statweb/. Accessed September 4, 2018.

36. Klein J, Dooper M. *Longziekten: feiten en cijfers 2013*. Amersfoort: Long Alliantie Nederland; 2013.

37. Medicines Evaluation Board (CBG). Trimbow 100 microgram/6 microgram/12,5 microgram per dosis aerosol, oplossing. Geneesmiddeleninformatiebank. https://db.cbg-meb.nl/ords/f?p=111:3::ATC:NO::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,120061. Published July 17, 2017. Accessed January 14, 2019.

38. Lambooij A, de Metz J, Essink R, et al. *Medicatie bij Astma en COPD*. Utrecht: NIVEL; 2016. https://nvl004.nivel.nl/nivel-2015/sites/default/files/bestanden/medicatie_bij_astma_en_copd.pdf. Accessed December 19, 2018.

39. Brusselle G, Price D, Gruffydd-Jones K, et al. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. *Int J Chron Obstruct Pulmon Dis*. 2015;10(Journal Article):2207-2217. doi:10.2147/COPD.S91694

40. Barnes N, Ishii T, Hizawa N, et al. The distribution of blood eosinophil levels in a Japanese COPD clinical trial database and in the rest of the world. *Int J Chron Obstruct Pulmon Dis*. 2018;13:433-440. doi:10.2147/COPD.S144108

41. Toledo-Pons N, Boven JFM van, Román-Rodríguez M, et al. ACO: Time to move from the description of different phenotypes to the treatable traits. *PLOS ONE*. 2019;14(1):e0210915. doi:10.1371/journal.pone.0210915

42. Cosio BG, Soriano JB, López-Campos JL, et al. Defining the asthma-COPD overlap syndrome in a COPD cohort. *Chest*. 2016;149(1):45-52.

43. van Boven JFM, Román-Rodríguez M, Palmer JF, Toledo-Pons N, Cosío BG, Soriano JB. Comorbidome, pattern, and impact of asthma-COPD overlap syndrome in real life. *Chest*. 2016;149(4):1011-1020.

44. Hospers JJ, Schouten JP, Weiss ST, Rijcken B, Postma DS. Asthma attacks with eosinophilia predict mortality from chronic obstructive pulmonary disease in a general population sample. *Am J Respir Crit Care Med*. 1999;160(6):1869-1874.

45. Hizawa N. LAMA/LABA vs ICS/LABA in the treatment of COPD in Japan based on the disease phenotypes. *Int J Chron Obstruct Pulmon Dis*. 2015;10(Journal Article):1093-1102. doi:10.2147/COPD.S72858

46. Nederland Z. Farmacotherapeutisch kompas. https://www.farmacotherapeutischkompas.nl/. Accessed November 23, 2018.

47. Rogliani P, Calzetta L, Matera MG, et al. Inhaled therapies and cardiovascular risk in patients with chronic obstructive pulmonary disease. *Expert Opin Pharmacother*. 2019;20(6):737-750. doi:10.1080/14656566.2019.1570133

48. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2018. doi:10.1002/14651858.CD012620.pub2

49. Calzetta L, Cazzola M, Matera MG, Rogliani P. Adding a LAMA to ICS/LABA Therapy: A Meta-analysis of Triple Combination Therapy in COPD. *Chest*. January 2019. doi:10.1016/j.chest.2018.12.016

50. Zorginstituut Nederland. *Guideline for Economic Evaluations in Healthcare*. Diemen; 2016. https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare. Accessed January 3, 2018.

51. Sato R, Rey GG, Nelson S, Pinsky B. Community-acquired pneumonia episode costs by age and risk in commercially insured US adults aged≥ 50 years. *Appl Health Econ Health Policy*. 2013;11(3):251-258.

52. Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB, Respiratory Effectiveness Group. Predicting frequent COPD exacerbations using primary care data. *Int J Chron Obstruct Pulmon Dis*. 2015;10(Journal Article):2439-2450. doi:10.2147/COPD.S94259

53. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1(3):199-209.

54. Watz H, Tetzlaff K, Wouters EFM, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med*. 2016;4(5):390-398. doi:10.1016/S2213-2600(16)00100-4

55. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). *Eur Respir J*. January 2015:ERJ-01360-2014. doi:10.1183/09031936.00136014

56. Nederlandse zorgautoriteit. DIS open data. http://www.opendisdata.nl/. Published 2018. Accessed November 6, 2018.

57. NIVEL. Hoe vaak komt COPD voor en bij wie? | NIVEL. https://www.nivel.nl/nl/nzr/aandoeningen-copd-hoe-vaak-komt-copd-voor-en-bij-wie. Published 2018. Accessed November 6, 2018.

58. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Eur Respir J*. January 2018:1801586. doi:10.1183/13993003.01586-2018

59. Rodrigo GJ, Price D, Anzueto A, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2017;12(Journal Article):907-922. doi:10.2147/COPD.S130482

60. Abrahams R, Bjermer L, Ferguson GT, et al. Characteristics of patients with and without chronic obstructive pulmonary disease exacerbations during the tiotropium/olodaterol TONADO studies. Poster presented at the: CHEST Annual Meeting 2016; October 2016; Los Angeles, CA, USA.

61. Hettle R, Wouters H, Ayres J, et al. Cost-utility analysis of tiotropium versus usual care in patients with COPD in the UK and Belgium. *Respir Med*. 2012;106(12):1722-1733. doi:10.1016/j.rmed.2012.09.006

62. Calverley PMA, Anzueto AR, Carter K, et al. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomised, parallel-group, active-controlled trial. *Lancet Respir Med*. 2018;6(5):337-344. doi:10.1016/S2213-2600(18)30102-4

63. Oba Y, Sarva ST, Dias S. Efficacy and safety of long-acting beta-agonist/long-acting muscarinic antagonist combinations in COPD: a network meta-analysis. *Thorax*. 2016;71(1):15-25. doi:10.1136/thoraxjnl-2014-206732

64. Rijksoverheid. Wet geneesmiddelenprijzen - BWBR0007867. https://wetten.overheid.nl/BWBR0007867/2013-01-01#Artikel1. Published January 1, 2013. Accessed November 6, 2018.

65. Tariq SM, Thomas EC. Maintenance therapy in COPD: time to phase out ICS and switch to the new LAMA/LABA inhalers? *Int J Chron Obstruct Pulmon Dis*. 2017;12(Journal Article):1877-1882. doi:10.2147/COPD.S138006

66. Vogelmeier C, Zhong N, Humphries MJ, et al. Indacaterol/glycopyrronium in symptomatic patients with COPD (GOLD B and GOLD D) versus salmeterol/fluticasone: ILLUMINATE/LANTERN pooled analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11(Journal Article):3189-3197. doi:10.2147/COPD.S116786

67. Ficker JH, Rabe KF, Welte T. Role of dual bronchodilators in COPD: A review of the current evidence for indacaterol/glycopyrronium. *Pulm Pharmacol Ther*. 2017;45(Journal Article):19-33.

68. Bjermer L, van Boven JFM, Costa-Scharplatz M, et al. Indacaterol/glycopyrronium is cost-effective compared to salmeterol/fluticasone in COPD: FLAME-based modelling in a Swedish population. *Respir Res*. 2017;18(1):206-017-0688-5. doi:10.1186/s12931-017-0688-5

69. Oba Y, Chandran AV, Devasahayam JV. Long-acting Muscarinic Antagonist Versus Inhaled Corticosteroid when Added to Long-acting beta-agonist for COPD: A Meta-analysis. *Copd*. 2016;13(6):677-685. doi:10.3109/15412555.2016.1170799

70. Vrijhoef HJ, Diederiks JP, Wesseling GJ, van Schayck CP, Spreeuwenberg C. Undiagnosed patients and patients at risk for COPD in primary health care: early detection with the support of non-physicians. *J Clin Nurs*. 2003;12(3):366-373.

71. Rogliani P, Matera MG, Ora J, Cazzola M, Calzetta L. The impact of dual bronchodilation on cardiovascular serious adverse events and mortality in COPD: a quantitative synthesis. *Int J Chron Obstruct Pulmon Dis*. 2017;12(Journal Article):3469-3485. doi:10.2147/COPD.S146338

72. Lucas AE, Smeenk FW, Smeele IJ, van Schayck CP. Overtreatment with inhaled corticosteroids and diagnostic problems in primary care patients, an exploratory study. *Fam Pract*. 2008;25(2):86-91. doi:10.1093/fampra/cmn006

73. de Miguel-Diez J, Carrasco-Garrido P, Rejas-Gutierrez J, et al. Inappropriate overuse of inhaled corticosteroids for COPD patients: impact on health costs and health status. *Lung*. 2011;189(3):199-206. doi:10.1007/s00408-011-9289-0

74. Poulos LM, Ampon RD, Marks GB, Reddel HK. Inappropriate prescribing of inhaled corticosteroids: are they being prescribed for respiratory tract infections? A retrospective cohort study. *Prim Care Respir J*. 2013;22(2):201-208. doi:10.4104/pcrj.2013.00036

Tables

Table 1: Input data for the BIA model

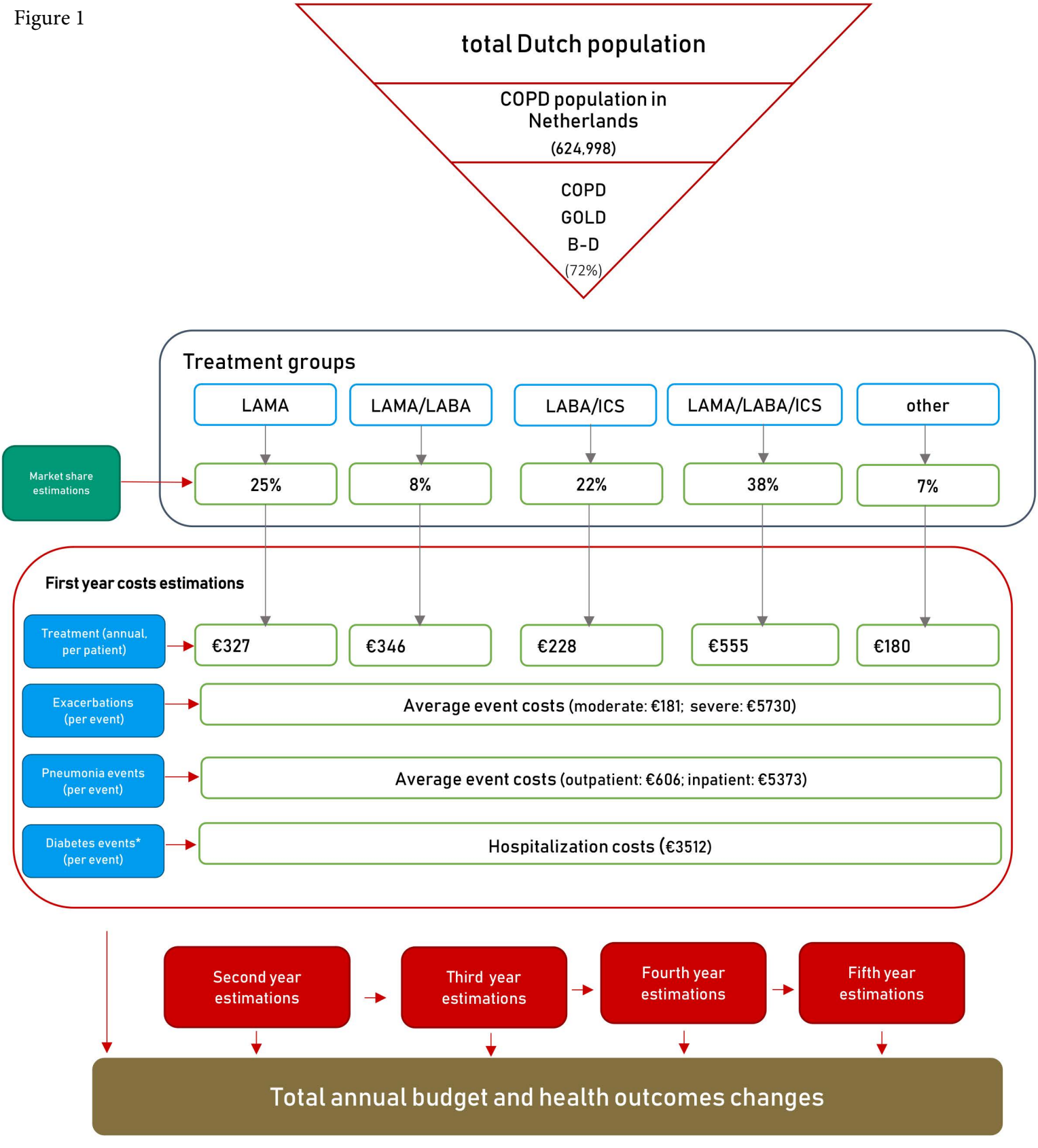
Population input data (2017)	**Population Size**	**Source**
COPD population in the Netherlands	624,988	[6]
Annual growth of COPD population	8,844	[6]
Eligible population GOLD B-D (% of total COPD population)	449,991 (72%)	[36]
Market shares of treatment types		
Current treatment mix	LAMA: 25.0% LABA/ICS: 21.8% LABA/LABA/ICS: 38.4% LABA/LAMA: 8.2% Other (LABA): 6.6%	[17,38]
New treatment mix	LAMA: 25.0% LABA/ICS: 5.5% LABA/LABA/ICS: 19.2% LABA/LAMA: 43.8% Other (LABA): 6.6%	
Cost inputs	**Costs (€, 2017)**	
Annual maintenance drug costs per patient	LAMA: 327 LABA/ICS: 228 LABA/LABA/ICS: 555 LABA/LAMA: 346 Other (LABA): 180	[17]

Exacerbations Moderate Severe	 181 5730	 31
Pneumonia event Inpatient Outpatient	 4,373 606	 56
Diabetes-related hospitalizations	3512	56
Clinical inputs	**Risk (per year)**	
Exacerbations	*Absolute exacerbation risk* Moderate: 0.31 Severe: 0.06 *Relative risk by therapy* LABA/LAMA: 1 (reference) LAMA: 1.04 LABA/ICS: 1.22 LAMA/LABA/ICS: 0.86 *Relative risk by exacerbation history* No prior exacerbation: 1 1 prior exacerbation: 2.55 2 or more prior exacerbations: 4.86	55,60 62 59 58 63 52 55,60
Pneumonia event Relative risk ICS users	Baseline (non-ICS users): 4.7%; RR (ICS users) : 1.31	21 59
Location of treatment	Outpatient: 72% ; Inpatient: 28%	51
Diabetes-related hospitalizations Prevalence in COPD patients	 Non-ICS users 4.5% ICS users: 6.0%	 23

	20.9%	[57]

COPD, Chronic Obstructive Pulmonary Disease; GOLD, The Global Initiative for Chronic Obstructive Lung Disease; LAMA, long-acting muscarinic antagonists; LABA, long-acting β2-agonists; ICS, inhaled corticosteroids.

Figure 1



*In scenario analysis only

Figure 2

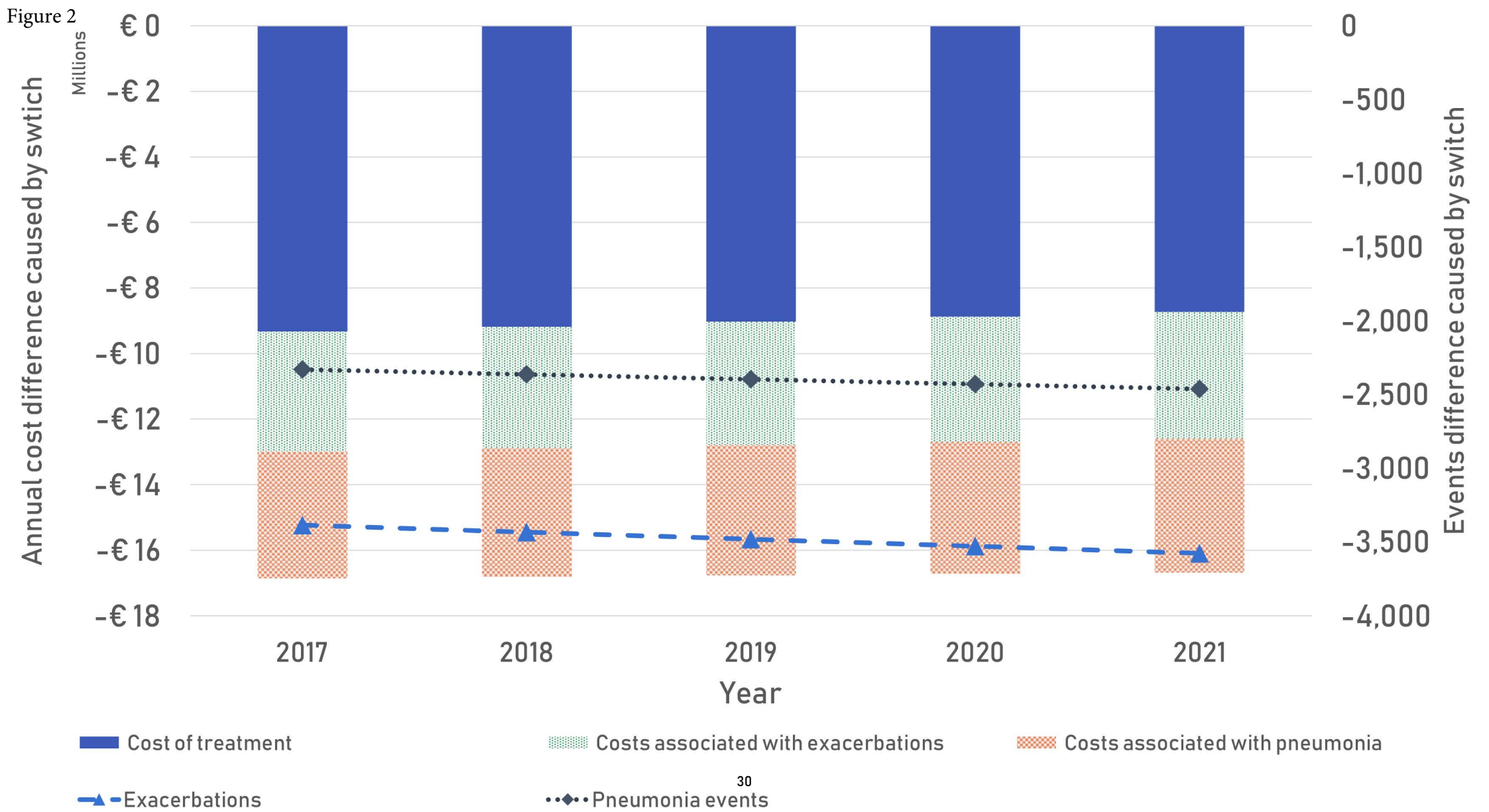

Millions
€ 0
-€ 2
-€ 4
-€ 6
-€ 8
-€ 10
-€ 12
-€ 14
-€ 16
-€ 18
Annual cost difference caused by swtich
0
-500
-1,000
-1,500
-2,000
-2,500
-3,000
-3,500
-4,000
Events difference caused by switch
2017
2018
2019
2020
2021
Year
Cost of treatment
Costs associated with exacerbations
Costs associated with pneumonia
Exacerbations
Pneumonia events

Figure 3

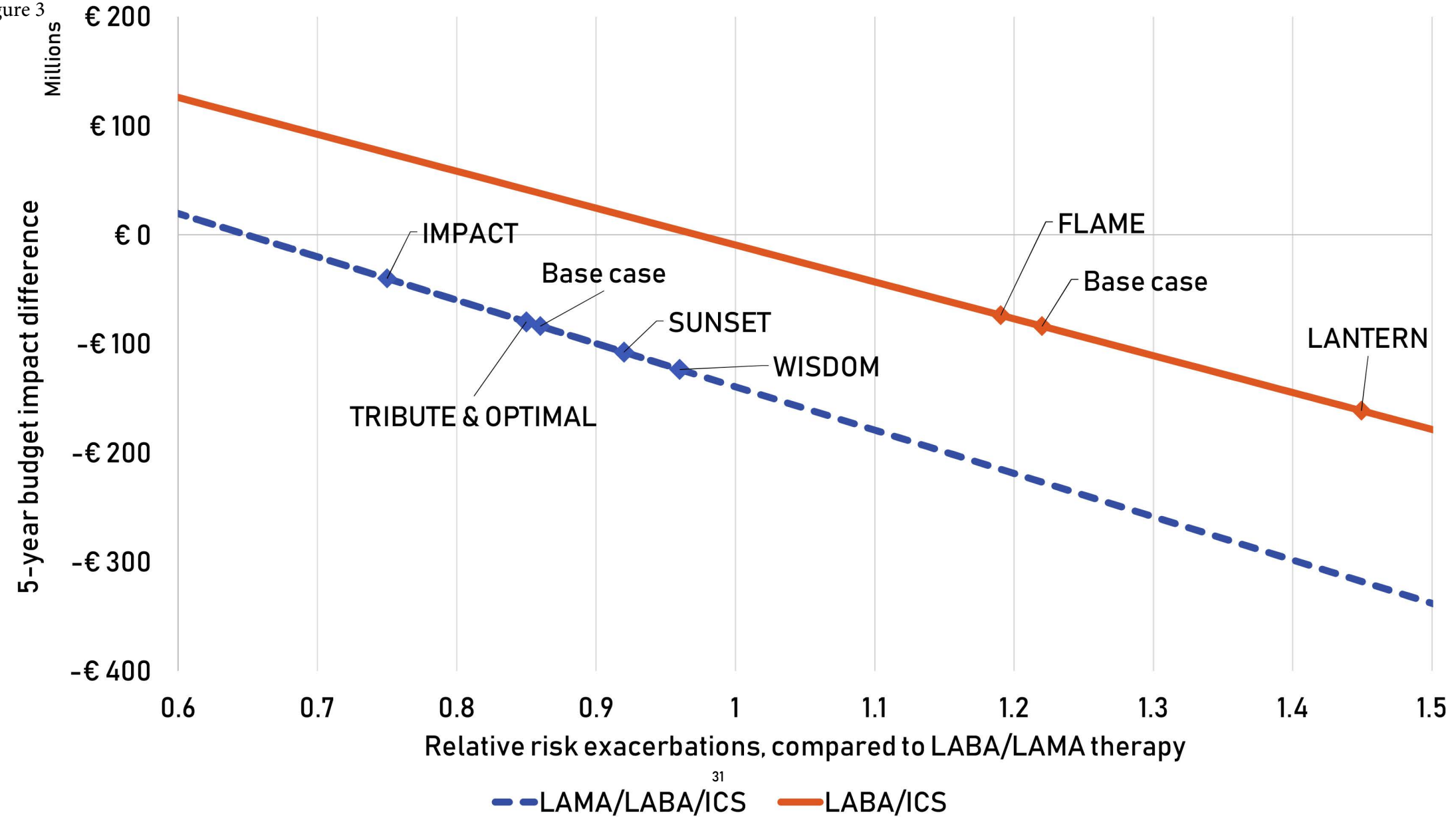

Millions
€ 200
€ 100
€ 0
-€ 100
-€ 200
-€ 300
-€ 400
5-year budget impact difference
IMPACT
Base case
SUNSET
WISDOM
TRIBUTE & OPTIMAL
FLAME
Base case
LANTERN
0.6
0.7
0.8
0.9
1
1.1
1.2
1.3
1.4
1.5
Relative risk exacerbations, compared to LABA/LAMA therapy
LAMA/LABA/ICS
LABA/ICS

Figure 4

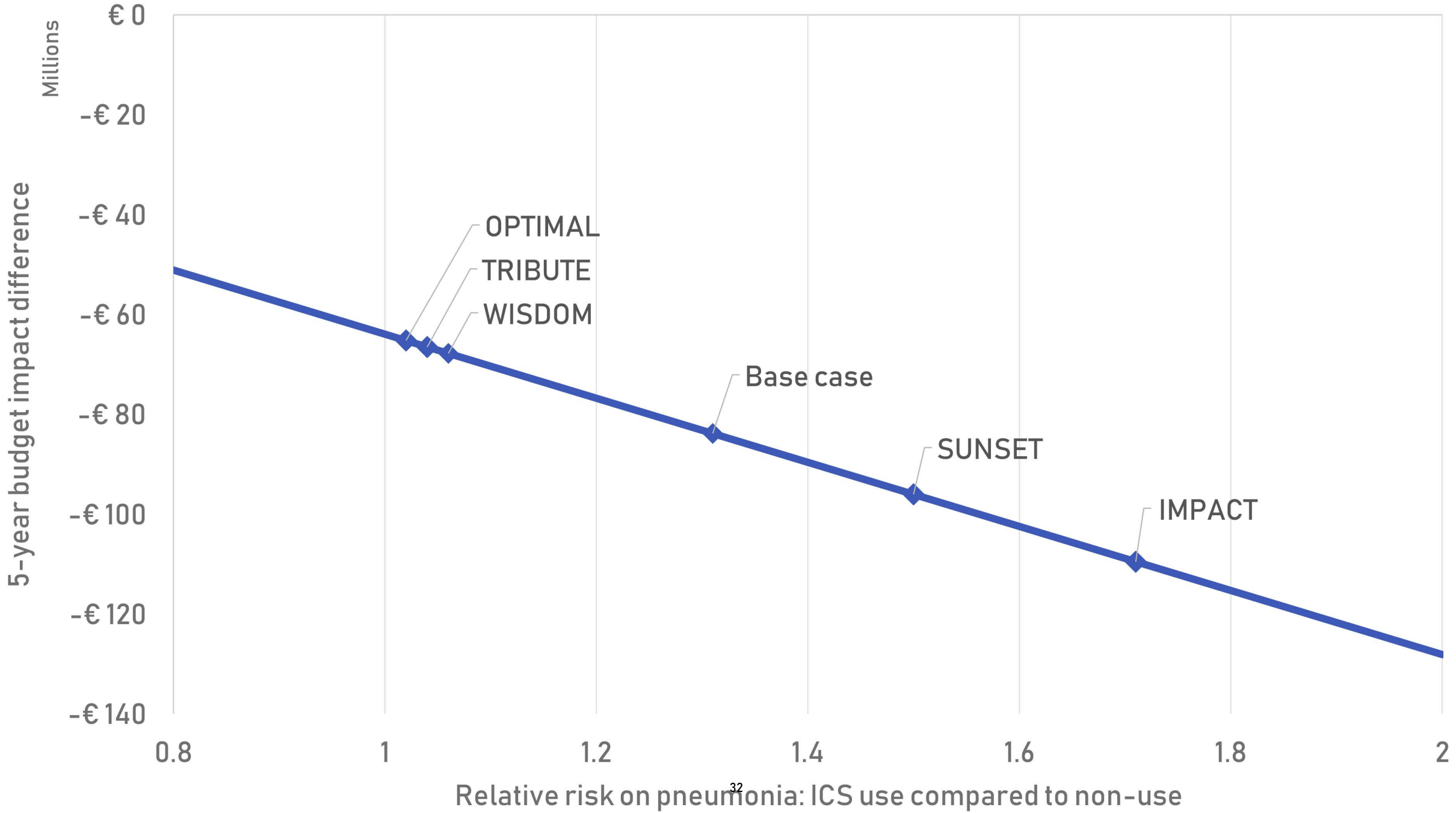
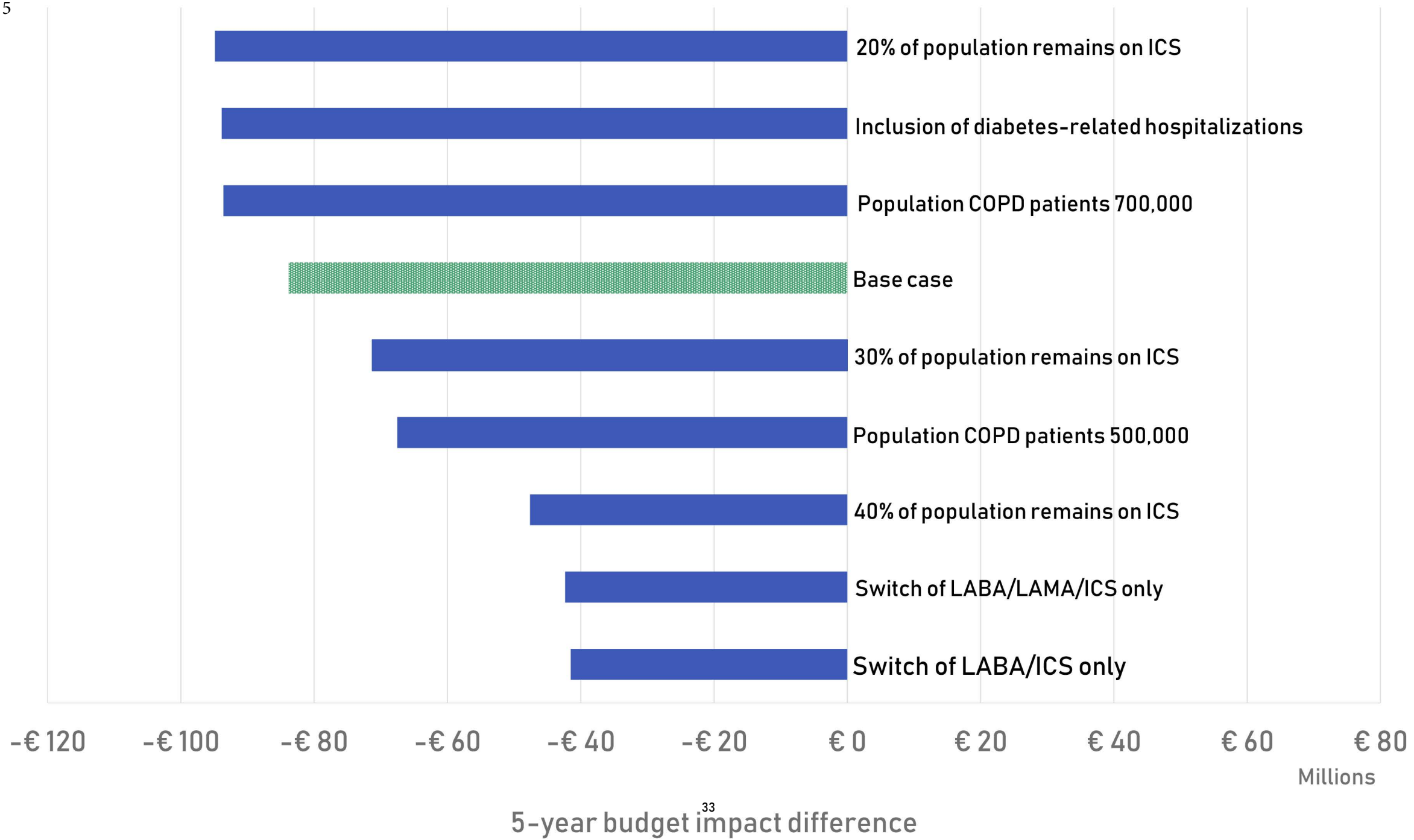

€ 0
-€ 20
-€ 40
-€ 60
-€ 80
-€ 100
-€ 120
-€ 140
Millions
5-year budget impact difference
OPTIMAL
TRIBUTE
WISDOM
Base case
SUNSET
IMPACT
0.8
1
1.2
1.4
1.6
1.8
2
Relative risk on pneumonia: ICS use compared to non-use

Figure 5


20% of population remains on ICS
Inclusion of diabetes-related hospitalizations
Population COPD patients 700,000
Base case
30% of population remains on ICS
Population COPD patients 500,000
40% of population remains on ICS
Switch of LABA/LAMA/ICS only
Switch of LABA/ICS only
-€ 120
-€ 100
-€ 80
-€ 60
-€ 40
-€ 20
€ 0
€ 20
€ 40
€ 60
€ 80
Millions
5-year budget impact difference

Supplementary appendix

Economic impact of reducing inappropriate inhaled corticosteroids use in patients with COPD: ISPOR's guidance on budget impact in practice

Contents

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Supplementary table 2-Overview of the disaggregated and total events 0

Supplementary table 3-Overview of the disaggregated annual and total costs and savings in euros 1

Supplementary table 1- ISPOR reporting format recommendations for BIA

Article segment	Structural elements	Content for reporting	Page where we reported the given segment
Introduction	Objectives	Clear and into a relation with the study perspectives.	3
	Epidemiology and management of health problem	Info about disease prevalence, incidence, severity, disease progression, undiagnosed or undertreated cases and relevant risk factors.	
	Clinical impact	Eligible population, existing management options and efficacy and safety.	
	Economic impact	Description on previous BIA for different intervention, treatment patterns and study for cost of care.	
Study design and methods	Design	Cost calculator (preferred approach), condition-specific cohort or individual simulation model.	4

	Patient population	Eligible population for the new intervention (estimation on local coverage, open population-entering leaving rates, proportion of subgroups-if relevant). Recommended data sources: budget holder's data, national or reginal data.	
	Intervention mix	Use and characteristics (indication, dose, efficacy, adverse events, and adherence) of the current and expected intervention mix (rates in tables describing the intervention mix). Recommended data sources, uptake rate and costs for *current Intervention mix*: budget's holder data or published info form registries, claims databases, local surveys, market research, secondary sources; uptake rate to be based on past changes, market research or clinical expert opinion; costs based on actual cost on the intervention for the budget holder (including discounts, rebates), administration and monitoring costs (local unit costs, or product labels and publications), and side effects/complications managing/withdrawal costs (rates form labels, and cost from published data or develop algorithms in consultations with physicians from the treatment field. *new intervention mix*: data from another jurisdiction where introduced or estimates of market share from the producer, or extrapolation on similar product diffusion in the budget holder's settings; and side effects/complications managing/withdrawal costs (rates form labels, and cost from published data or develop algorithms in consultations with physicians from the treatment field).	

	Time horizon	Presented and justified. Common period 1-5 years.	
	Perspective	Clear inclusion of cost categories and intended audience. Recommended-Budget holder perspective.	
	Analytic framework description	Complete description of the model structure as well as being graphically presented (flow diagram). Input values and alternative scenarios. Description of any computations/transformations with assessment of straightness and weakness, as well as selection criteria for the literature inputs.	5
	Input data Data Sources	Methods for primary data collection including the forms/questionnaires.	6-8

	Data collection	Description of the calculations and justification of the choice of the scenarios. Recommendation: indirect cost should not be included; no discounting.	
	Analyses	Described and justified. Disaggregated presentation BIA for each budget period from the time horizon.	
	Uncertainty	Relevant: parameter (efficacy of current and new intervention) and structural (changes in expected intervention patterns) uncertainty- facing limited data obstacles.	9
Results	Budget period resource use	Table displaying change in use for each time period (intervention use, intervention side effects, condition related).	10
	Costs		10

	Uncertainty analyses and Scenario analyses	Table/graphic displaying total and disaggregated costs for each time period (pharmacy/physician visit, in/out/home-patient care). Figures/ tables capturing the key elements of the BIA –Tornado diagrams.	11-12
Conclusions and Limitations	Main conclusion	Based on the results.	14
	Limitations	Design aspects, off-label use, adherence assumptions, completeness and quality of data inputs and sources.	13-14

Supplementary table 2-Overview of the disaggregated and total events

	2017	2018	2019	2020	2021	Total
Number of COPD exacerbations						
Baseline scenario	349,389	354,333	359,277	364,221	369,165	1796385
Switch scenario	346,004	350,900	355,796	360,692	365,588	1778980
Difference	-3,385	-3,433	-3,481	-3,529	-3,577	-17405
Number of events related to poor diabetes control (included as scenario, excluded from the base case)						
Baseline scenario	5,106	5,178	5,250	5,322	5,395	26251
Switch scenario	4,602	4,667	4,732	4,797	4,862	23660
Difference	-504	-511	-518	-525	-532	-2591
Number of LRTI/pneumonia events						
Baseline scenario	25,097	25,452	25,807	26,162	26,517	129034
Switch scenario	22,766	23,088	23,410	23,732	24,054	117050
Difference	-2,331	-2,364	-2,397	-2,430	-2,463	-11984

Supplementary table 3-Overview of the disaggregated annual and total costs and savings in euros

	2017	2018	2019	2020	2021	Total
Baseline scenario costs						
TOTAL	€ 592,330,427	€ 595,448,061	€ 598,578,920	€ 601,724,745	€ 604,887,159	€ 2,992,969,312
Cost of treatment	€ 173,026,189	€ 170,210,387	€ 167,407,810	€ 164,620,198	€ 161,849,175	€ 837,113,759
Costs associated with exacerbations	€ 377,636,748	€ 382,980,562	€ 388,324,375	€ 393,668,189	€ 399,012,002	€ 1,941,621,876
Costs associated with pneumonia	€ 41,667,490	€ 42,257,113	€ 42,846,735	€ 43,436,358	€ 44,025,981	€ 214,233,677
Switch scenario costs						
TOTAL	€ 575,472,232	€ 578,635,160	€ 581,810,599	€ 585,000,196	€ 588,205,489	€ 2,909,123,676
Cost of treatment	€ 163,696,615	€ 161,032,641	€ 158,381,178	€ 155,743,874	€ 153,122,265	€ 791,976,574
Costs associated with exacerbations	€ 373,977,914	€ 379,269,953	€ 384,561,991	€ 389,854,030	€ 395,146,069	€ 1,922,809,956
Costs associated with pneumonia	€ 37,797,703	€ 38,332,566	€ 38,867,429	€ 39,402,292	€ 39,937,155	€ 194,337,146
Cost difference						
TOTAL	-€ 16,858,195	-€ 16,812,902	-€ 16,768,322	-€ 16,724,549	-€ 16,681,670	-€ 83,845,636
Costs of treatment	-€ 9,329,574	-€ 9,177,746	-€ 9,026,631	-€ 8,876,323	-€ 8,726,910	-€ 45,137,185
Costs associated with exacerbations	-€ 3,658,834	-€ 3,710,609	-€ 3,762,384	-€ 3,814,159	-€ 3,865,934	-€ 18,811,919
Costs associated with pneumonia	-€ 3,869,786	-€ 3,924,546	-€ 3,979,306	-€ 4,034,066	-€ 4,088,826	-€ 19,896,532